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Temporal trends in colorectal cancer mortality in Greece, 2014-2022: a Joinpoint regression analysis

Vasilios Papastergiou[a,b], John Souglakos[c], George Karamanolis[d], Gregorios Paspatis[e], Gregory Chlouverakis[b]

"Evangelismos-Polykliniki" General Hospitals of Athens; University Hospital of Crete Medical School, Heraklion; National and Kapodistrian University of Athens, Aretaieion Hospital, Athens; School of Health Sciences, University of Ioannina; School of Medicine, University of Crete, Heraklion, Greece

Abstract

Background Colorectal cancer (CRC) is the second most deadly cancer worldwide; however, data on CRC mortality in Greece remain scarce. This study aimed to evaluate temporal trends in CRC mortality in Greece between 2014 and 2022, focusing on sex- and age-groups.

Methods CRC mortality and demographics were gathered from the Hellenic Statistical Authority (ELSTAT). Age-adjusted mortality rates (AAMRs) were calculated, using age-specific mortality rates standardized to the WHO standard population. For age subgroups, crude mortality rates were analyzed. Temporal trends were established using Joinpoint regression with estimation of annual percent change (APC).

Results During the study period, there were 24,973 CRC-related deaths (14,201 men, 56.8%). The overall AAMRs were 10.7 [95% confidence interval (CI) 10.3-11.1] per 100,000 population in 2014 and 10.2 (95%CI 9.7-10.6) in 2022, exhibiting no significant change (APC -0.62, 95%CI -1.34 to 0.13; P=0.11). Men had consistently higher AAMRs than women throughout the study. The AAMRs for women significantly declined between 2014 and 2022 (APC -1.02, 95%CI -1.98 to -0.03; P=0.03). Contrarily, the decline was not significant in men (APC -0.35, 95%CI -1.34 to 0.67; P=0.48). All age subgroups for both sexes exhibited declining trends, except for men 45-59 years who showed a non-significant uptrend throughout the study, and men <45 years who showed a significant increase between 2017 and 2022.

Conclusions In Greece, CRC mortality significantly declined between 2014 and 2022 in women, although not in men. Increasing trends observed in younger men warrant further consideration, aiming to optimize prevention and outcomes of CRC.

Keywords Colorectal cancer, mortality, temporal trends, Joinpoint regression, Greece

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Correspondence to: Vasilios Papastergiou, MD, Department of Gastroenterology, Evangelismos-Polykliniki General Hospital of Athens, Athens, Ipsilantou 45-47, 10676, Athens, Greece, e-mail: vasi.pap@hotmail.com

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Introduction

Colorectal cancer (CRC) remains a significant global health concern, projected to increase to 3.2 million new cases and 1.6 million deaths by 2040 [1,2]. The incidence of CRC exhibits substantial variability between countries, correlating positively with the Human Development Index (HDI). Indeed, the incidence rates of CRC in countries with a very high HDI are about 4 times those of countries with a low HDI [3]. A combination of environmental and genetic factors contributes to CRC risk, including lifestyle, dietary habits, family history and metabolic health conditions [4]. Despite continuous advancements in detection and treatment, CRC remains the third most common malignancy and the second most deadly

cancer worldwide [3]. Nevertheless, CRC is also one of the most preventable cancers and is a major target of organized screening programs that aim to effectively reduce CRC-related mortality [5]. In Greece, CRC is the third most frequent cancer type among men and the second among women, accounting for 9% of total cancer deaths [6]. Historically, colonoscopy screening has been offered on an opportunistic basis in Greece, whereas national data on CRC incidence and outcomes remain scarce. Recently, a Hellenic population-based CRC screening program was launched, funded through the European Union's (EU) Recovery and Resilience Fund, although evidence on its rollout is not yet available. Further healthcare interventions are probably warranted, aiming to reduce avoidable mortality from CRC. Evaluation of CRC mortality is of utmost importance for health policy planning, although it has never been explored systematically in Greece. Hence, the present study aimed to evaluate temporal trends in CRC mortality in Greece between 2014 and 2022, focusing on sex- and age-groups.

Materials and methods

Data sources

CRC mortality and demographic information between January 01, 2014, and December 31, 2022, were gathered from national data published by the Hellenic Statistical Authority (ELSTAT). The death registration system records death information based on the international classification of diseases 10 (ICD-10) standard. CRC patients were identified using ICD-10 diagnostic codes C18-C21 (including colon, rectosigmoid junction, rectum, anus and anal canal). Evaluation of a longer period was not feasible, as the ICD-10 coding was officially adopted in Greece on January 1st 2014 and mortality data after 2022 were not yet available at the time of the analyses. For census years (e.g., 2021), population counts were taken from the corresponding Population-Housing Census. For non-census years, population data were derived from ELSTAT's official annual estimates of the resident population, calculated by updating census counts with births, deaths and net migration, in accordance with national and EU statistical standards.

Statistical analysis

Age-adjusted mortality rates (AAMRs) of CRC per 100,000 population, with their 95% confidence intervals (95%CIs), were calculated for the study, using the 2001 World Health Organization (WHO) standard population [7]. For each year under consideration, the overall and sex-specific rates were analyzed. To reflect clinically and epidemiologically meaningful stages in CRC risk, screening and mortality patterns, age was stratified as follows: <45, 45-59, 60-74 and >74 years old. For age subgroups, crude mortality rates (CMRs) of CRC per 100,000 age-specific population were calculated, with 95%CIs. Temporal trends were assessed using the Joinpoint Regression Program (Version 5.4.0.0.; National Cancer Institute, Bethesda, MD, USA), allowing estimation of the annual percent change (APC) with corresponding 95%CIs. Both AAMRs and CMRs were log-transformed prior to model fitting, in accordance with software recommendations. Given the 9-year study period, the maximum number of joinpoints was set to 1. Model selection was performed using the weighted Bayesian information criterion (BIC) [8], while 95%CIs and P-values for APC estimates were calculated using the empirical quantile method; these are the default methods in version 5.4.0.0. [9]. The models were fitted using the observed (unsmoothed) mortality rates, and APC estimates were reported only for statistically significant joinpoint models. Trends were classified as increasing or decreasing when the APC differed significantly from 0 (2-sided P<0.05). Since the initial residual plots of the fitted models against time indicated potential serial autocorrelation, models were adjusted to incorporate first-order autoregressive errors, ensuring valid estimation of temporal trends and corresponding CIs. The present study follows a methodology similar to that in previously published reports evaluating temporal trends in cancer mortality [10,11].

Results

Between 2014 and 2022, a total of 24,973 people died from CRC in Greece, of whom 14,201 (56.8%) were men. The total number of deaths, AAMRs and estimated APC from 2014-2022, overall and by sex, are summarized in Table 1. The overall AAMRs for CRC were 10.7 (95%CI 10.3-11.1) per 100,000 population in 2014 and 10.2 (95%CI 9.7-10.6) in 2022, exhibiting no significant change (APC -0.62, 95%CI -1.34 to 0.13; P=0.11) (Fig. 1). After stratification by sex, men had consistently higher AAMRs than women throughout the study. The AAMRs for women significantly declined from 8.4 (95%CI 7.8-8.9) in 2014 to 7.4 (95%CI 6.9-7.8) in 2022, showing an APC reduction of -1.02 (95%CI -1.98 to -0.03; P=0.03). However, the decline was not significant in men, who had AAMRs of 13.7 (95%CI 12.9-14.4) in 2014 and 13.6 (95%CI 12.8-14.3) in 2022 (APC -0.35, 95%CI -1.34 to 0.67; P=0.48).

Detailed data concerning the total number of deaths and CMRs according to age categories, overall and by sex, are provided in Supplementary Table 1. Considering the overall population, no statistically significant temporal trends were detected by age-stratified analyses (Table 2, Fig. 2). Trends were declining, except in the age-group <45 years, which showed a non-significant uptrend (APC 0.64, 95%CI -5.06 to 6.82; P=0.85). Among women, CMRs declined steadily for all age-groups,

[a]Department of Gastroenterology, "Evangelismos-Polykliniki" General Hospitals of Athens (Vasilios Papastergiou); [b]Department of Biostatistics, School of Medicine, University of Crete, Heraklion (Vasilios Papastergiou, Gregory Chlouverakis); [c]Laboratory of Translation Oncology, University Hospital of Crete Medical School, Heraklion (John Souglakos); [d]Department of Endoscopy, 2 Academic Surgical Unit, National and Kapodistrian University of Athens, Aretaieion Hospital (George Karamanolis); [e]Department of Gastroenterology, University Hospital and Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina (Gregorios Paspatis), Greece

Table 1 Annual total number of deaths, annual age-adjusted colorectal cancer mortality rates and estimated annual percent changes in Greece, overall and by sex, 2014-2022

Sex	Year	Total number of deaths	AAMR (per 100,000)	95%CI	APC (2014-2022, %)	95%CI for APC	P-value
Men	2014	1553	13.7	12.9-14.4	-0.35	-1.34 to 0.67	0.48
	2015	1583	13.5	12.7-14.1			
	2016	1643	14.0	13.2-14.7			
	2017	1509	12.6	11.9-13.2			
	2018	1551	13.0	12.3-13.7			
	2019	1570	13.2	12.5-13.9			
	2020	1592	13.2	12.5-13.9			
	2021	1583	12.9	12.3-13.6			
	2022	1617	13.6	12.8-14.3			
Women	2014	1197	8.4	7.8-8.9	-1.02	-1.98 to -0.03	0.03
	2015	1222	8.0	7.5-8.5			
	2016	1248	8.3	7.7-8.8			
	2017	1177	8.2	7.6-8.7			
	2018	1130	7.6	7.1-8.1			
	2019	1281	8.5	7.9-9.0			
	2020	1182	7.8	7.3-8.3			
	2021	1192	7.8	7.3-8.3			
	2022	1143	7.4	6.9-7.8			
Overall	2014	2750	10.7	10.3-11.1	-0.62	-1.34 to 0.13	0.11
	2015	2805	10.5	10.1-10.9			
	2016	2891	10.8	10.4-11.3			
	2017	2686	10.1	9.6-10.5			
	2018	2681	10.0	9.6-10.4			
	2019	2851	10.6	10.2-11.1			
	2020	2774	10.2	9.8-10.7			
	2021	2775	10.1	9.7-10.6			
	2022	2760	10.2	9.7-10.6			

AAMR, age-adjusted mortality rate; APC, annual percent change; CI, confidence interval

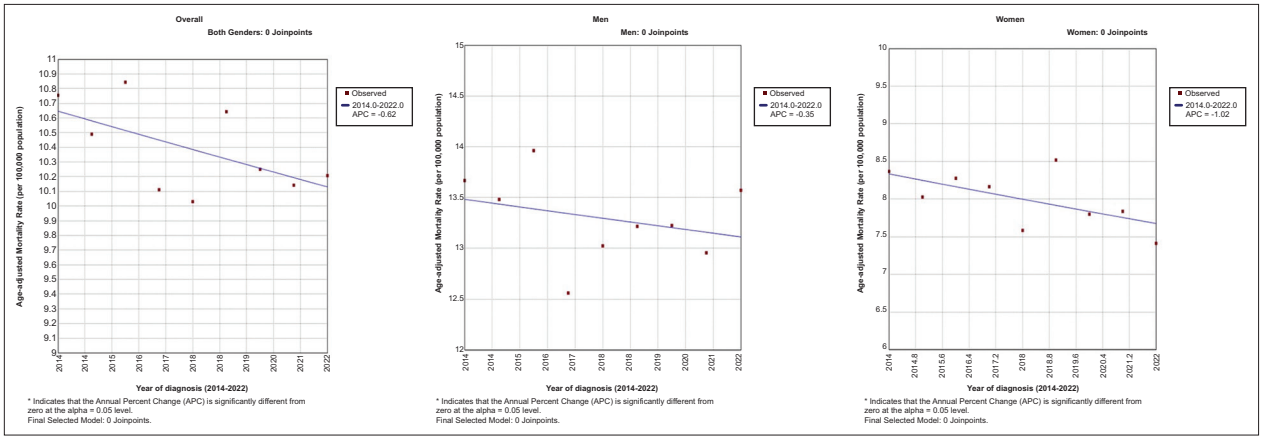

Figure 1 Joinpoint regression curve showing WHO age-adjusted mortality rates for colorectal cancer per 100,000 population in Greece, 2014-2022

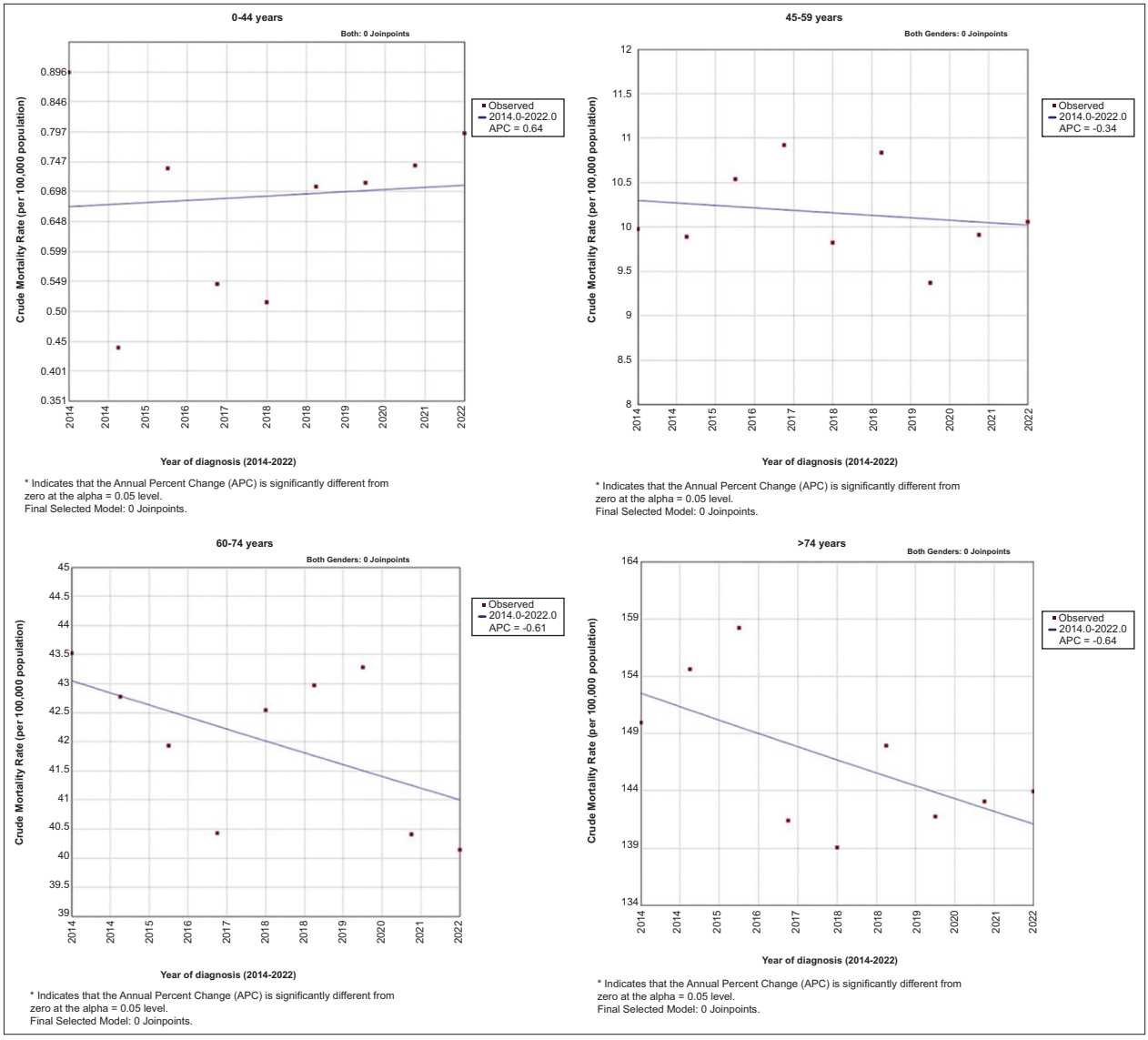

Figure 2 Joinpoint regression curve for colorectal cancer mortality by age-group per 100,000 population in Greece, 2014-2022

although not at a statistically significant level (Table 2, Fig. 3). A non-significant declining trend was also shown for older men, in the 60-74 and >74 age groups (Table 2, Fig. 4). Contrarily, men aged 45-59 years exhibited a non-significant uptrend throughout the study (APC 0.26, 95%CI -1.60 to 2.18; P=0.77). The CMRs for men aged <45 years exhibited a biphasic pattern, with a significant decline from 2014-2017 (APC -21.91, 95%CI -44.51 to -2.80; P=0.02), followed by a significant increase from 2017-2022 (APC 18.90, 95%CI 6.22-58.70; P=0.008).

Discussion

To the best of our knowledge, this is the first report assessing national CRC-related mortality trends in Greece. The study covered a 9-year period (2014-2022), and included extensive age- and sex-stratified analyses. The AAMRs calculated in the present study closely reassemble those estimated previously, supporting the validity of our findings. In a recent study utilizing data from the International Agency for Research on Cancer's (IARC) GLOBOCAN 2020 project, the respective rate for CRC mortality (year 2020) in Greece was 10.7 per 100,000 individuals (men: 14.1, women: 7.8) [12]. These rates are comparable or even slightly lower compared to the overall AAMRs reported at a European level (12.3) and those from other Southern European countries, including Italy (10.2), Portugal (13.0) and Spain (11.5). Various factors may affect CRC mortality at a country level, including differences in dietary habits, healthcare infrastructure, access to screening, early detection and treatment, as well as the prevalence of modifiable risk factors (e.g., smoking and obesity) [13,14]. Apparently, CRC incidence in Greece remains relatively low compared to most other EU countries, despite the fact that

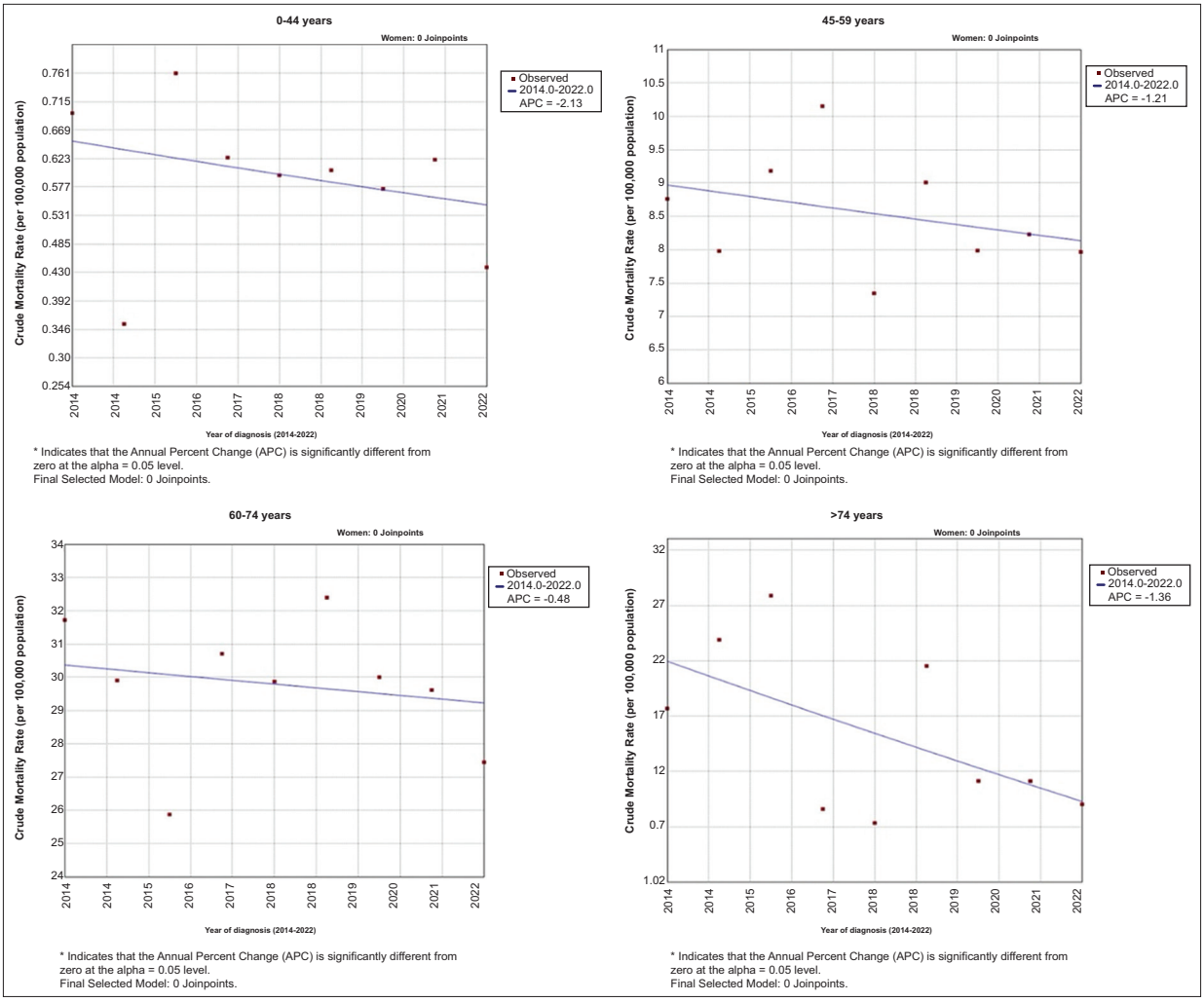

Figure 3 Joinpoint regression curve for colorectal cancer mortality by age-group in women per 100,000 population in Greece, 2014-2022

Table 2 Joinpoint regression analysis of crude colorectal cancer mortality rates in Greece, by sex- and age-group, 2014-2022

Sex	Age-group (years)	Joinpoint period	APC (%)	95%CI	P-value
Men	0-44	2014-2017	-21.91	-44.51 to -2.80	0.02
		2017-2022	18.90	6.22 to 58.70	0.007
	45-59	2014-2022	0.26	-1.60 to 2.18	0.77
	60-74	2014-2022	-0.66	-1.98 to 0.73	0.34
	>74	2014-2022	-0.66	-1.60 to 0.30	0.15
Women	0-44	2014-2022	-2.13	-8.37 to 4.40	0.44
	45-59	2014-2022	-1.21	-5.46 to 3.15	0.47
	60-74	2014-2022	-0.48	-2.40 to 1.60	0.62
	>74	2014-2022	-1.36	-3.36 to 0.69	0.17
Overall	0-44	2014-2022	0.64	-5.06 to 6.82	0.85
	45-59	2014-2022	-0.34	-1.96 to 1.33	0.66
	60-74	2014-2022	-0.61	-1.79 to 0.59	0.27
	>74	2014-2022	-0.97	-2.08 to 0.20	0.09

APC, annual percent change; CI, confidence interval

the country fares relatively poorly with respect to smoking, overweight and obesity, and considering that a population-based CRC screening program was lacking during the study [6]. As previously observed [12,15], the CRC mortality rates are consistently higher in men, highlighting the need for targeted interventions, aiming to equitably address CRC mortality for both sexes.

By joinpoint regression, the AAMRs of CRC followed a declining trend in Greece between 2014 and 2022, although this was only statistically significant among women. Congruently, a recent study evaluating CRC mortality in the EU using the WHO database predicted favorable AAMRs in 2024 compared to those observed in 2015-2019, with the decline being consistently higher for women (11.8%) than for men (6.9%) [16]. Differences in CRC outcomes have been documented between women and men, probably attributable to various factors [17]. These include differences in anatomical profiles and molecular disease, as well as in the efficacy and safety of treatments for CRC. In addition, women tend to adhere to CRC screening at a higher rate than do men [18,19], although not universally [20]. During the study, colonoscopy

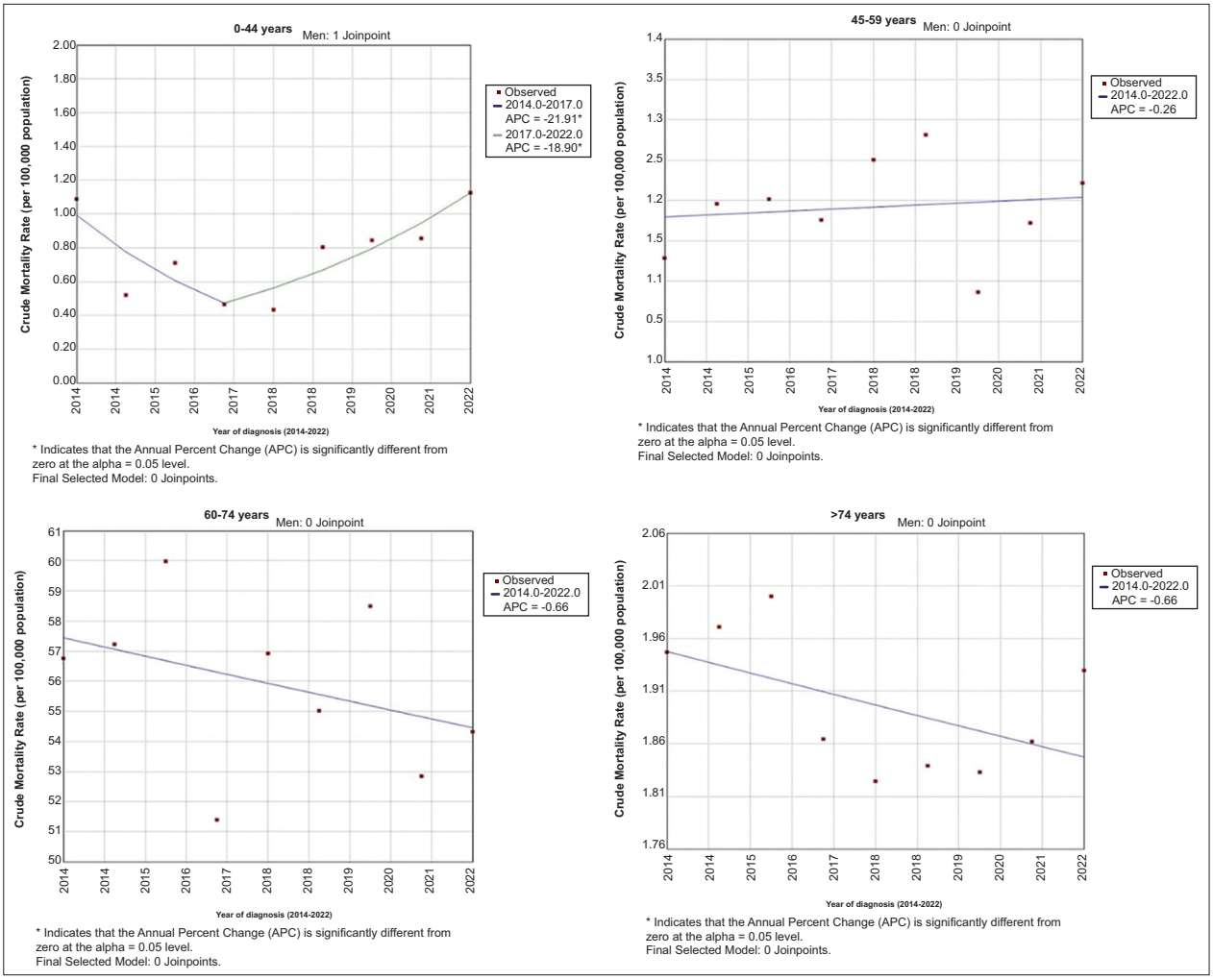

Figure 4. Joinpoint regression curve for colorectal cancer mortality by age-group in men per 100,000 population in Greece, 2014-2022

screening in Greece was offered opportunistically. In the absence of utilization data, the extent to which screening colonoscopy may have influenced the observed declining trends remains uncertain. Downward trends in CRC mortality have also been observed in other Southern European countries, such as Italy [21] and Spain [22]. Contrarily, certain Balkan countries (e.g., Croatia, Serbia and Bulgaria) apparently exhibit increasing trends, probably linked to rising economic development and potentially lower screening uptake [23].

The increase in CRC mortality trends among younger men is an important finding from the present study. Although mortality in men aged <45 years declined from 2014-2017, a sharp increase was noted thereafter, during the 6-year period from 2017-2022 (APC 18.90, P=0.008). Clearly, these findings should be interpreted cautiously, as the relatively small number of deaths in the 0-44 years age-group may have introduced substantial rate instability, potentially inflating APC estimates. Nevertheless, a non-significant uptrend with an APC of +0.26 was also depicted throughout the study for men aged 45-59 years. Even more importantly, these findings are indirectly supported by prior observations indicating that CRC is no longer an old-age disease [24,25]. Since the 1990s, incidence and mortality from CRC have been steadily rising in young adults in the United States [26,27], while a similar trend has been observed in Europe [28]. Possible explanations include increasing rates of obesity during adolescence, prolonged sedentary behavior and dietary patterns that are now more common in childhood and adolescence, such as high consumption of sugar beverages, red and processed meats, and western-style diets. Importantly, early-onset CRC tends to be more aggressive [29,30]. Thus, the United States Preventive Service Task Force recommended lowering the threshold for average-risk CRC screening to 45 years [31]. In Europe, the CRC AAMRs also appear to follow an increasing trend with age 25-49, for both sexes in Italy (+1.5% in men, +2.6% in women) and the United Kingdom (+26.1% in men, +38.6% in women), among Polish (+5.9%) and Spanish (+5.5%) men, and among German women (+7.2%) [16].

Using data from the Regional Cancer Registry of Crete (the only population-based cancer registry available in Greece), Sifaki-Pistolla *et al* observed a significant rising trend for CRC on the island of Crete for adults aged <50 years during

the period 1992-2021, especially after 2001 [32]. More specifically, the mean age-specific incidence rate presented a 29.6% increase from 2001-2011 in the age-group 20-34 years, while a further increase of 42.8% was predicted from 2022-2030. For individuals aged <50 years, greater body mass index and body surface area, smoking measured in pack/years, heavy alcohol consumption and farming occupation were positively correlated with the risk of CRC. In Europe, screening programs are heterogeneous, mostly targeting individuals aged 50-74 years [33]. Thus, further efforts should be made to develop updated policies and population-based guidelines, taking into account the worrisome rise in CRC among younger adults. In contrast to younger subjects, CRC incidence and mortality have generally been decreasing in older adults [34]. We observed the highest decline in CRC mortality among the oldest (>74 years) age group (APC -0.94). This finding also aligns with previous data, where the highest percent mortality decline in the EU was among individuals ≥70 years (-11.6% for men and -15.9% for women) [16].

The present study is not free from limitations. Mortality statistics based on ICD coding should be interpreted cautiously, as incomplete or inconsistent death certification may have biased the reported mortality rates. However, this study used official, public and national-representative data, collected using a vigorous methodology. Furthermore, no known changes in coding or certification practices occurred during the study, reducing the likelihood of bias in the observed trends. As in previous assessments of CRC mortality [35,36], deaths from anal cancer (coded C21) were included, although this cancer has a tumor biology different to CRC. This was due to the fact that ICD codes C18-C21 are reported as a unified cause of death by the ELSTAT, not allowing for sub-site assessments. However, the contribution of anal cancer to mortality is expected to be minimal, given that this cancer is far less lethal [37] and the proportion of anal cancers is generally <5% [38]. Importantly, subgroup analyses were limited to age and sex; thus, several other factors (e.g., family and CRC screening history, lifestyle risk-factors, comorbidities, stage at CRC diagnosis) were not assessed. Consequently, while the findings suggest increasing mortality among younger men, causal inferences or implications for lowering the average-risk CRC screening threshold in Greece cannot be drawn. A further complexity is added by the inclusion of the COVID-19 period. Pandemic-related disruptions to screening, diagnosis and treatment may have contributed to excess CRC mortality from 2020 onwards, potentially influencing the observed trends. Patients with early-onset CRC often experience longer pre-diagnostic delays, presenting with more advanced disease [39]. Thus, accentuated diagnostic delays during the COVID-19 period could, at least partly, explain the post-2017 increase in mortality observed among men <45 years. Importantly, opportunistic colonoscopy screening was offered in Greece during the study; thus, nationwide screening rates were not recorded. Probably, the COVID-19 pandemic negatively affected colonoscopy screening; however, any effect on CRC mortality would be expected to occur over a multi-year latency period, mostly affecting individuals in the screening age range (i.e., 50-75 years). Finally, the 9-year study period may be insufficient for detecting modest temporal trends using joinpoint regression, a method that is conservative by design, while no formal statistical tests (e.g., confidence interval overlap) were conducted for between-sex APC comparisons.

In conclusion, this is the first study evaluating national CRC mortality trends in Greece. From 2014-2022, a significant decline was observed for women, although not for men. By age-stratified analyses, increasing mortality trends were observed for younger men, particularly in those aged <45 years from 2017 onwards. These findings should be considered by public health experts and policymakers, aiming to optimize the prevention and outcomes of CRC in Greece.

Summary Box

What is already known:

- Colorectal cancer (CRC) remains a significant global health concern and the second most deadly cancer worldwide
- CRC is one of the most preventable cancers and a major target of disease prevention programs
- Although evaluation of mortality trends is a critical indicator for health policy planning, national data and temporal trends in CRC mortality in Greece remain poorly investigated

What the new findings are:

- The overall age-adjusted mortality rates (AAMRs) for CRC in Greece were 10.7 per 100,000 population in 2014 and 10.2 in 2022, exhibiting no significant change
- Men had consistently higher AAMRs than women throughout the study; between 2014 and 2022, CRC mortality in Greece significantly declined in women, although not in men
- Analyses by age subgroups revealed increasing mortality trends for younger men, particularly in those aged <45 years from 2017 onwards

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Supplementary material

Supplementary Table 1 Annual total number of deaths and crude colorectal cancer mortality rates in Greece according to age category, overall and by sex, 2014-2022

Age group (years)	Year	Men			Women			Overall		
		Total number of deaths	CMR (per 100,000)	95%CI	Total number of deaths	CMR (per 100,000)	95%CI	Total number of deaths	CMR (per 100,000)	95%CI
0-44	2014	32	1.1	0.7-1.4	20	0.7	0.4-1.0	52	0.9	0.6-1.1
	2015	15	0.5	0.2-0.8	10	0.3	0.1-0.6	25	0.4	0.2-0.6
	2016	20	0.7	0.4-1.0	21	0.7	0.4-1.0	41	0.7	0.5-0.9
	2017	13	0.5	0.2-0.7	17	0.6	0.3-0.9	30	0.5	0.3-0.7
	2018	12	0.4	0.2-0.7	16	0.6	0.3-0.9	28	0.5	0.3-0.7
	2019	22	0.8	0.5-1.1	16	0.6	0.3-0.9	38	0.7	0.4-0.9
	2020	23	0.8	0.5-1.2	15	0.5	0.2-0.8	38	0.7	0.4-0.9
	2021	23	0.9	0.5-1.2	16	0.6	0.3-0.9	39	0.7	0.5-0.9
	2022	29	1.1	0.7-1.5	11	0.4	0.1-0.7	40	0.8	0.5-0.9
45-59	2014	122	11.3	9.3-13.3	102	8.7	7.0-10.4	224	9.9	8.6-11.2
	2015	130	11.9	9.9-14.0	94	8.0	6.3-9.6	224	9.8	8.5-11.1
	2016	131	12.0	9.9-14.1	109	9.2	7.4-10.9	240	10.5	9.2-11.8
	2017	129	11.8	9.7-13.7	121	10.1	8.3-11.9	250	10.9	9.5-12.2
	2018	138	12.5	10.4-14.6	88	7.3	5.8-8.8	226	9.8	8.5-11.1
	2019	142	12.8	10.7-14.9	108	9.0	7.3-10.7	250	10.8	9.4-12.1
	2020	121	10.8	8.9-12.8	96	8.0	6.3-9.5	217	9.3	8.1-10.6
	2021	131	11.7	9.7-13.7	99	8.2	6.6-9.8	230	9.9	8.6-11.1
	2022	141	12.2	10.2-14.2	95	7.9	6.3-9.5	236	10.0	8.7-11.3
60-74	2014	461	56.7	51.5-61.9	289	31.7	28.0-35.3	750	43.5	40.4-46.6
	2015	467	57.2	52.0-62.4	274	29.9	26.3-33.4	741	42.7	39.7-45.8
	2016	495	59.9	54.6-65.2	240	25.8	22.6-29.1	735	41.9	38.9-44.9
	2017	430	51.4	46.5-56.2	290	30.7	27.1-34.2	720	40.4	37.4-43.3
	2018	482	56.9	51.8-62.0	287	29.8	26.4-33.3	769	42.5	39.5-45.5
	2019	472	55.0	50.0-59.9	317	32.4	28.8-35.9	789	42.9	39.9-45.9
	2020	507	58.4	53.3-63.5	298	30.0	26.5-33.4	805	43.2	40.2-46.3
	2021	460	52.8	48.0-57.6	297	29.6	26.2-32.9	757	40.4	37.5-43.2
	2022	482	54.3	49.4-59.1	272	27.4	24.1-30.7	754	40.1	37.2-43.0
>74	2014	938	194.7	182.2-207.1	786	117.6	109.4-125.9	1724	149.9	142.8-157.0
	2015	971	197.1	184.7-209.4	844	123.9	115.5-132.2	1815	154.6	147.5-161.7
	2016	997	200.0	187.5-212.4	878	127.8	119.4-136.3	1875	158.2	151.0-165.3
	2017	937	186.4	174.5-198.3	749	108.6	100.8-116.3	1686	141.4	134.6-148.1
	2018	919	182.4	170.6-194.2	739	107.3	99.5-115.0	1658	139.0	132.3-145.7
	2019	934	183.9	172.1-195.7	840	121.5	113.3-129.7	1774	147.9	141.0-154.8
	2020	941	183.3	171.6-195.0	773	111.1	103.2-118.9	1714	141.7	135.0-148.4
	2021	969	186.2	174.5-197.9	780	111.1	103.3-118.	1749	143.0	136.3-149.7
	2022	965	192.9	180.8-205.1	765	109.0	101.3-116.7	1730	143.9	137.1-150.7

CMR, crude mortality rate; CI, confidence interval